Sounding the Alarm about Cadmium-Related Bone Loss

Challenge

One in eight Americans is 65 or older. As our society ages, research into the health problems associated with aging, such as bone loss, is taking center stage. Osteoporosis is a major cause of disability in elderly persons, with hip fracture often triggering the dreaded transition to a dependent lifestyle.

In healthy bone, a balance exists between the rates of bone formation and bone resorption. After skeletal growth has stopped, a new equilibrium is reached that typically results in a slow, age-dependent net loss of bone mineral in humans. Cadmium can accelerate this net loss of bone mineral, increasing the incidence of osteoporosis in the elderly. For example, women who smoke cigarettes, which contain cadmium, often experience increased bone loss, especially after menopause.

Argonne's Response

Argonne scientists have demonstrated that cadmium causes a release of calcium from bone in both mice and dogs at blood concentrations below current Occupational Safety and Health Administration (OSHA) standards for cadmium exposure (see table). Permissible exposure levels for cadmium do not protect against cadmium-induced bone loss because occupational limits are set to protect against cadmium's potential to cause cancer and kidney damage. Argonne showed — for the first time — that the bone loss response begins within hours of the first exposure to cadmium, well before the onset of the classical kidney damage that cadmium is known to cause (Figure 1).

Argonne's studies of cadmium-related bone loss were the first to clearly show that maternal animals, during pregnancy and lactation, and female animals, after removal of their ovaries (to simulate human menopause), were more susceptible to bone loss after exposure than were nonpregnant intact controls. Specifically, Argonne has shown that the early bone response to cadmium involves increased expression of enzymes involved in bone resorption. The Laboratory's Biosciences staff have identified genes responsible for the cellular response to cadmium and are working to further delineate the specific cell-signaling pathways involved.

Cadmium Exposure Levels in Perspective

Group	Blood Cadmium Concentration
Start of bone response, dogs	2–5 µg/L
Nonsmokers	0.26 ± 0.03 µg/L
Smokers (≥ 20 cigarettes/day)	2.5 ± 1.5 µg/L
Battery plant workers	22 µg/L
OSHA action level	5 µg/L

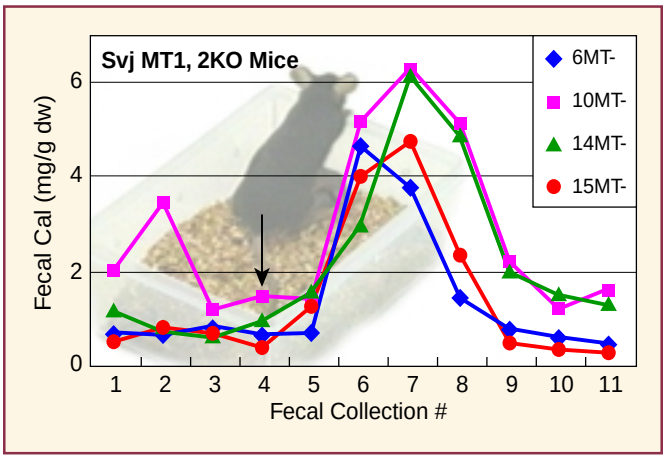

Figure 1. Bone response to cadmium. Single oral cadmium dose, given at arrow above, caused transient increase in bone calcium excretion in mice feces. (Each line represents results from individual mouse [total of four mice].)

Approach

Argonne's analyses of animal bone cell cultures have shown that at very low concentrations — lower than the OSHA-acceptable blood level of 5 µg/L — cadmium almost immediately stimulates the formation and activity of osteoclasts (Figure 2). Osteoclasts are

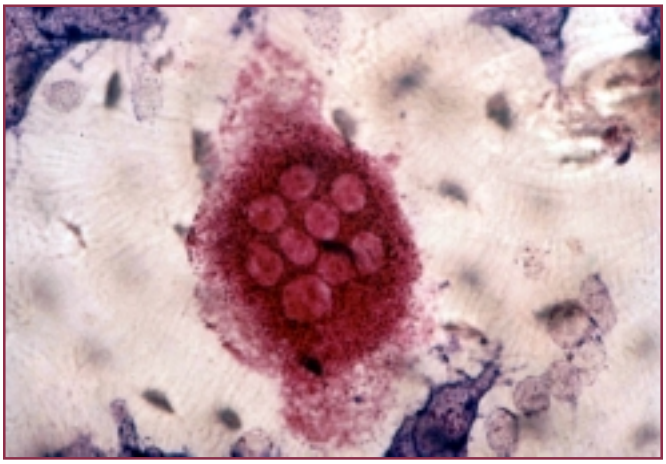

Figure 2. Multinucleated osteoclast — the cell that dissolves bone mineral and collagen matrix.

large multinucleated cells that attach to bone, dissolve its mineral, and break down the collagen matrix to release calcium into the bloodstream. To determine the mechanism by which cadmium causes bone loss, researchers looked for which bone cell genes changed in their expression after exposure to cadmium. They isolated RNA from mouse bones 2 or 4 hours after exposure by ingestion; the sampling was timed so that it would occur before the onset of bone demineralization.

Observing which bone cell genes change in their expression after exposure to cadmium helps scientists find out how cadmium causes bone loss. RNA isolated from mouse bones 2 or 4 hours after exposure by ingestion was subjected to a microarray analysis that contained probes for about 8,500 mouse genes — nearly the entire mouse genome — as well as differential display analysis to monitor changes in gene expression.

"The remarkable power of this approach is that we can query an organism's entire genome to devise one specific new hypothesis."

says principal researcher Maryka Bhattacharyya.

Results

Argonne's research has shown that cadmium activates two types of gene expression pathways in bone cells early after exposure — protective pathways that counteract the toxic effects of cadmium (including metallothionein induction) and toxic-response pathways involved in stimulation of osteoclast-mediated bone resorption (Figure 3). The researchers also discovered a gene of unknown function that increased 18-fold within 4 hours after cadmium exposure; they plan to clone and sequence this gene to determine its role in the bone cell's response to cadmium.

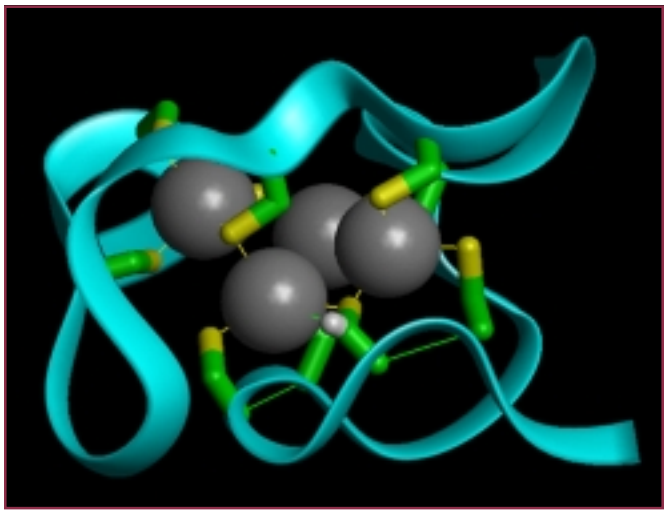

Figure 3. Cadmium causes the body to produce more metallothionein. This protein tightly binds cadmium in the cytoplasm, keeping it away from the bone cell's toxic response sites.

Collaborators

Benedictine University
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